provided for the Examiner's convenience, and shall not be construed as submission of a re-presented claim set under 37 CFR §1.121. No new matter was added by these amendments.

A. Rejections Addressed from December 13, 2001 Office Action (OA)

(1) Rejection of claims 2, 3, 5, 22 and 24 under 35 U.S.C. §101

Claims 2, 3, 5, 22 and 24 were rejected under 35 U.S.C. §101 because the claimed invention "is not supported by either a specific asserted utility or well established utility." (OA, p. 2) Applicant respectfully traverses this rejection as it applies to remaining claims 2, 3, 5, 22 and 24.

To be considered useful under 35 U.S.C. §101, an invention must have a specific, substantial and credible utility. It is well established "when a properly claimed invention meets at least one stated objective, utility under §101 is clearly shown." (*Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 958 (CAFC 1983)). That is, only a single utility for an invention needs be disclosed in a patent application to satisfy the 35 U.S.C. §101 utility requirement.

In making this rejection the Office states:

> Applicants argue that the polynucleotides of the invention constitute probes that have a diagnostic utility due to their chromosomal localization at 3q21.1-p13....[T]he invention spans over a quite large fragment of chromosome 3 (3q21.1-p13 region of chromosome 3) and no specific localization is provided allowing determination of where the probe actually hybridizes, and if the site corresponds to a marker for a specific disease characterized, for example by a specific deletion or mutation....There is no evidence that LOH (loss of heterozygosity) is associated with the polynucleotide of the present invention....although chromosomal deletions and translocations are associated with various tumors (see for example Cigurosa...there is no nexus between the claimed nucleid acid and any known deletion, nor sufficient information to allow the use of the claimed nucleic acid for the detection of any deletion or other alteration associated with any known tumor or other condition. (OA, p. 3-4)

Applicant respectfully disagrees with this contention as the specification has indeed asserted utility. One of skill in the art upon reading the specification would immediately appreciate that the polynucleotides of the present invention are located at a specific chromosomal location wherein translocations are associated with human disease; and would immediately appreciate that the polynucleotides could serve as a useful diagnostic for detecting and analyzing translocations and other genetic abnormalities at that locus. Applicant further provides the

Declaration under 37 CFR §1.132 of Dr. Theodore E. Whitmore as further evidence of this utility. One of skill in the art would immediately appreciate that the polynucleotides of the present invention have specific asserted and well-established utility. Moreover, the Office has not presented a preponderance of evidence to refute such assertions of utility.

The instant claims are drawn to inventive polynucleotides. As disclosed in the specification, from page 71, line 33 to page 74, line 7, the polynucleotides of the present invention can serve as diagnostics for human chromosome 3 abnormalities, particularly at the specific locus where the z219c gene is located, 3p14.2, within the 3p21.1-p13 region. As further disclosed in the specification and known by one of skill in the art, applicant emphasizes that translocation and loss of heterogeneity (LOH) at the specific 3p14.2 locus are gross chromosomal abnormalities that clearly associated with human disease, such as cancers (e.g., see page 73, lines 7-35; Declaration under 37 CFR §1.132 of Dr. Theodore E. Whitmore; and references of record), and hence the polynucleotides of the present invention can be used specifically as a diagnostic.

Not in Spec

In addition to the arguments of record, Applicant points the Office toward the Declaration under 37 CFR §1.132 of Dr. Theodore E. Whitmore as further evidence of this utility. Dr. Whitmore provides further experimental evidence that define a more precise locus for z219c within the 3p21.1-p13 region, i.e., at chromosome 3p14.2, as well as assertions that one of skill in the art would readily recognize the utility of a chromosome marker within the 3p21.1-p13 region or 3p14.2 locus. He further states:

> *It is well recognized that gross chromosomal aberrations such as deletions, LOH, and translocations in the 3p21.1-p13 region of chromosome 3 are associated with human cancers. In addition, it is well established that gross chromosomal aberrations such as deletions, LOH, and translocations in the 3p14.2 locus, wherein the z219c gene is located is associated with human cancers.* For example, the fragile histidine triad gene, FHIT, which maps to 3p14.2 (Ohta, M. et al, Cell 84: 587-597, 1996, copy enclosed), is also positioned in the same interval and between the same proximal and distal markers as z219c. This indicates that z219c is in close proximity to FHIT gene (±270 kb) and the most common of the constitutive aphidicolin-inducible fragile sites, FRA3B, of which the FHIT gene is a part (Ohta, M et al., supra.). The FRA3B fragile site locus is included in an approximate 200 to 300 kb specific region of chromosome 3p14.2 that is homozygously deleted in multiple tumor-derived cells lines and associated with renal cell carcinoma (Ohta, M et al., supra. ; and Wang, N. et al., Cancer Genet. Cytogenet. 11: 479-481, 1984, copy enclosed). Aberrant transcripts of the FHIT locus have also been found in approximately 50% of esophageal, stomach, and colon carcinomas (Ohta, M et al., supra.) as well as lung cancers of the small cell (SCLC) and nonsmall cell (NSCLC) type (Sozzi, G. et al., Cell 85: 17-26, 1996, copy enclosed). *The presence of diseases*

associated with gross chromosomal aberrations such as translocations and rearrangements within 3p14.2, the refined locus of z219c gene, further support the initial observations that z219c polynucleotide probes can serve as a diagnostic for gross chromosomal aberrations such as deletions, LOH, and translocations and rearrangements as described in the patent application.

The patent application discusses the use of z219c polynucleotide probes to detect chromosomal abnormalities on Chromosome 3 (page 71, line 33, to page 74 line, 7; page 72 lines 12-30). *More specifically, it is recognized in the art that the region in which z219c is localized, 3p21.1-p13 region, and more specifically, the 3p14.2 locus is a common hot spot for translocation (i.e., gross chromosomal rearrangement) and large deletions (e.g., described above) seen in human cancers, particularly renal cell carcinomas, including nonpapillary, papillary and oncocytomas (Shridhar, V. et al, Oncogene, 12:1931-1939, 1996, cited in the specification, show that chromosome 3p breakage, translocation and LOH at 3p14 is common in renal cell carcinomas, including nonpapillary, papillary and oncocytomas): and hereditary renal cell carcinoma (3p14 translocation breakpoint and loss, Shridhar, R. et al, Cancer Res., 56:5576-5578, 1996 cited in specification (Copy of record). The additional experimentation I have performed further narrows the locus for 219c, demonstrating that it is not unreasonable that one could use z219c polynucleotide probes as a diagnostic, to detect chromosomal abnormalities on Chromosome 3 to detect such common gross chromosomal abnormalities in and around the 3p14.2 locus, such as chromosomal translocations or rearrangements commonly seen in these human cancers.*

The 3q21.1-p13 locus, and more specifically the 3p14.2 locus, would be immediately appreciated by one of skill in the art as a critical region for translocations involved in human malignancies and tumors. Such information is disclosed in the application at page 71, line 33, to page 74 line, 7; page 72 lines 12-30, and it would be readily apparent to one reading this application that the z219c polynucleotides disclosed in the application could be used in for such purposes. As a person who recognizes the usefulness and need of additional chromosomal markers in diagnosing human disease, I recognize that the utility of new markers in this region of chromosome 3, such as the z219c polynucleotides disclosed in the application. *Using z219c polynucleotides as a chromosomal and cancer diagnostic is not unreasonable, and is in fact desirable, as multiple polynucleotide markers within a region add to the specificity and information surrounding the chromosomal aberration in question and cancer diagnosis.* (Affidavit, paragraphs 5 and 6, emphasis added))

Thus, contrary to the beliefs of the Office, gross chromosomal aberrations, such as rearrangements and translocations are indeed associated with cancers occur at the specific z219c locus, i.e., there is indeed a nexus between specific chromosomal aberrations for which the z219c polynucleotides of the present invention would detect and specific human disease (cancer). As such, Applicant has indeed asserted a specific utility for the polynucleotides of the present

invention as a chromosomal marker and probe. Moreover, it is well settled in the art how to use such polynucleotides as probes to detect and analyze chromosomal aberrations in the 3p21.1-p13 region of chromosome 3, which include the more specific locus of 3p14.2, is discussed and enabled in the specification (page 71, line 33 to page 74, line 7). Moreover, said utility is substantial and credible, as it is well known in the art that diagnostics for genetic diseases and tumors are sought after, and they are currently used in present day medicine to diagnose genetic disease or malignancy, or carriers or those susceptible to genetic disease, or to assist physicians in analyzing disease.

Applicant has shown that the polynucleotides of the present invention are more precisely localized to 3p14.2, and have provided the Declaration under 37 CFR §1.132 of Dr. Theodore E. Whitmore as further evidence utility. Dr. Whitmore provides further experimental evidence that define a more precise locus for z219c within the 3p21.1-p13 region, i.e., at chromosome 3p14.2, as well as assertions that one of skill in the art would readily recognize the utility of a chromosome marker within the 3p21.1-p13 region or 3p14.2 locus.

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Applicant has presented evidence in the specification, references in the art, as well as a Declaration under 37 CFR §1.132 of Dr. Theodore E. Whitmore, a skilled artisan, as further evidence of specific utility. One of skill would immediately appreciate that polynucleotide probes as markers within this locus, such as the z219c polynucleotides of the present invention, are useful for detecting and analyzing rearrangements, translocations and LOH involved in human malignancies and tumors. Translocations, rearrangements, deletions and LOH within chromosomal locus 3q21.1-p13, and more specifically 3p14.2 wherein the z219c gene is located were known at the time of filing to be associated with human disease, and research has continued to show that this locus is involved in human disease (e.g., see Response dated July 17, 2001). Applicant has provided evidence that gross chromosomal abnormalities in and around the specific z219c locus of 3p14.2 are clearly associated with human disease, and hence shown that the polynucleotides of the present invention are supported by a specific asserted utility that is substantial and credible.

The Office has not appreciated that the polynucleotides of the present indeed map to a specific site that is useful for the purposes of 35 USC §101. That specific site is 3p14.2 which is within the range presented in the specification (3p21.1-p13). However, the utilities

asserted in the specification are consistent with the more precisely define locus - that the polynucleotides of the present invention can be used as a chromosomal marker and diagnostic for human cancers and malignancies associated with chromosome 3 gross abnormalities such as translocations and rearrangements within 3p21.1-p13 region, and more specifically 3p14.2 locus. Moreover, as detailed above, Applicant has provided further evidence that gross chromosomal abnormalities within 3p21.1-p13, and more specifically 3p14.2, such as translocations and rearrangements, are clearly associated with human disease, and hence shown that the polynucleotides of the present invention are supported by a specific asserted utility that is substantial and credible.

Thus, since the z219c gene maps to this critical region involved in human malignancy and tumors, z219c polynucleotide probes of the present invention can be used to detect abnormalities or genotypes associated with 3p14.2 translocation, deletion LOH, and the like, described above. Moreover, the specific utility of z219c polynucleotides to detect such large chromosomal aberrations is clearly described in the specification at pages page 71, line 33 to page 74, line 7 and more specifically at. 72 line 12-30. Moreover, this utility is asserted and is well-established, as one of ordinary skill would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., because of the property of these polynucleotides having a 3p14.2 chromosomal localization).

Claims 2, 3, 5, 22 and 24 are indeed supported by a specific asserted utility that is substantial and credible. This is all 35 U.S.C. §101 requires. Consequently, the rejection of claims 2, 3, 5, 22 and 24 should be properly withdrawn.

(2) Rejection of claims 2, 3, 5, 22 and 24 under 35 U.S.C. §112, First Paragraph (Utility)

Claims 2, 3, 5, 22 and 24 were rejected under 35 U.S.C. §112, First Paragraph because "since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (OA, p. 5). The Office believes that one skilled in the art would not know how to use the claimed invention because it is alleged that the claimed invention is not supported by either a specific and substantial utility or a well established utility, citing the reasons set forth in the rejection under 35 USC § 101.

This ground of rejection is traversed. All claims are believed to be supported by either a specific and substantial asserted utility or a well established utility for the reasons discussed in Part A(1) above.

The polypeptides of the present invention are useful, and therefore one of skill in the art could make and use the invention. This is all 35 U.S.C. §112, First Paragraph requires. Consequently, the rejection under 35 U.S.C. §112, First Paragraph, of claims 2, 3, 5, 22 and 24 should be properly withdrawn.

(3) Rejection of claim 10 ***under 35 U.S.C. §112, First Paragraph*** *(New Matter)*

Claim 10 was rejected under 35 U.S.C. §112, First Paragraph "As containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (OA. p. 5) The Office requests a corrected version of the claim pending allowance. Because there appears to be confusion, Applicant has canceled claim 10 and rewritten it as claim 25 providing a corrected version of the claim and to clarify any misunderstanding about what the language of the claim is. Support for this amendment is provided in the specification at page 14, lines 11-15, page 34, lines 2-4, and original claim 10. No new matter was added by these amendments.

The new claim 25 should be allowable as was the original claim 10. The signal sequence of z219c is from amino acid 1 (Met) to 21 (Met) of SEQ ID NO:2 (see page 14, lines 11-15; and page 34 lines 2-4; and original claim 10), as stated in newly added claim 25. The claim 25 of the instant response is properly stated without error, and there is no new matter presented in correcting this error. Claim 25 does not constitute new matter, and was described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Consequently, the rejection under 35 U.S.C. §112, First Paragraph, as it may apply to newly added claim 25 should be properly withdrawn.

(4) General lack of evidence and support in making rejections.

Furthermore, Applicant respectfully emphasizes that no argument by the Office has been supported, nor data or evidence been cited or presented by the Office in making the instant rejections, aside from those apparent facts that are based on the personal knowledge of an employee of the Office, i.e., the Examiner. Applicant has provided evidence presented in the specification, twelve references in the art, as well as further evidence of a skilled artisan in asserting the utility of the inventive polynucleotides as well as further evidence of specificity of the chromosomal locus to which the polynucleotides of the present invention are localized. The Examiner in rejecting the utility of the polynucleotides of the present invention has merely concluded based on apparent facts that are based on the Examiner's personal knowledge (without presentation of a preponderance of the evidence) that the specific region to which z219c maps is "a quite large fragment of chromosome 3" (OA, p. 3) "no nexus between the claimed nucleic acid and any known deletion" and "a general region" (OA, p. 4) without considering all the evidence presented. Applicant is hereby respectfully requesting the Examiner to provide an affidavit under 37 CFR §1.104(d)(2) which states: "When a rejection in an application is based on facts within the personal knowledge of an employee of the Office, the data shall be as specific as possible, and the reference must be supported, when called for by the applicant, by the affidavit of such employee, and such affidavit shall be subject to contradiction or explanation by the affidavits of the applicant and other persons." Applicant further notes that in the December 13, 2001 Office Action, that this request was not addressed by the Office, nor was further data or evidence cited or presented by the Office in making the instant and former 35 U.S.C. §101 rejection.

Early reconsideration and allowance of the pending claims is respectfully requested. If the Patent Examiner believes that a telephone interview would expedite prosecution of this patent application, please call the undersigned at (206) 442-6676.

Respectfully Submitted,

Darrell C. Conklin, et al.

Jennifer K. Johnson, J.D.

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EXPLANATION OF AMENDMENTS WITH MARKINGS

IN THE CLAIMS

Please cancel claim 10 without prejudice to the prosecution thereof in a subsequent or continuing application.

~~10. A DNA construct encoding a fusion protein, the DNA construct comprising:~~

~~a first DNA segment encoding a polypeptide comprising a sequence of amino acid residues 1 (Met) through 25 (Gly) of SEQ ID NO:2; and~~

~~a second DNA segment encoding an additional polypeptide,~~

~~wherein the first and second DNA segments are connected in-frame; and~~

~~encode the fusion protein.~~

Please add the following new claim:

--25. A DNA construct encoding a fusion protein, the DNA construct comprising:

a first DNA segment encoding a polypeptide comprising a sequence of amino acid residues 1 (Met) through 21 (Met) of SEQ ID NO:2; and

a second DNA segment encoding an additional polypeptide,

wherein the first and second DNA segments are connected in-frame; and

encode the fusion protein.--

Enclosures:

Amendment Fee Transmittal (in duplicate)

Petition and Fee for 3 Month Extension of Time (in duplicate)

37 CFR § 1.132 affidavit of Dr. Theodore E. Whitmore (4 pages)

Notice of Appeal (in duplicate)

Appendix (2 pages)

Copy of references (3 references)

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